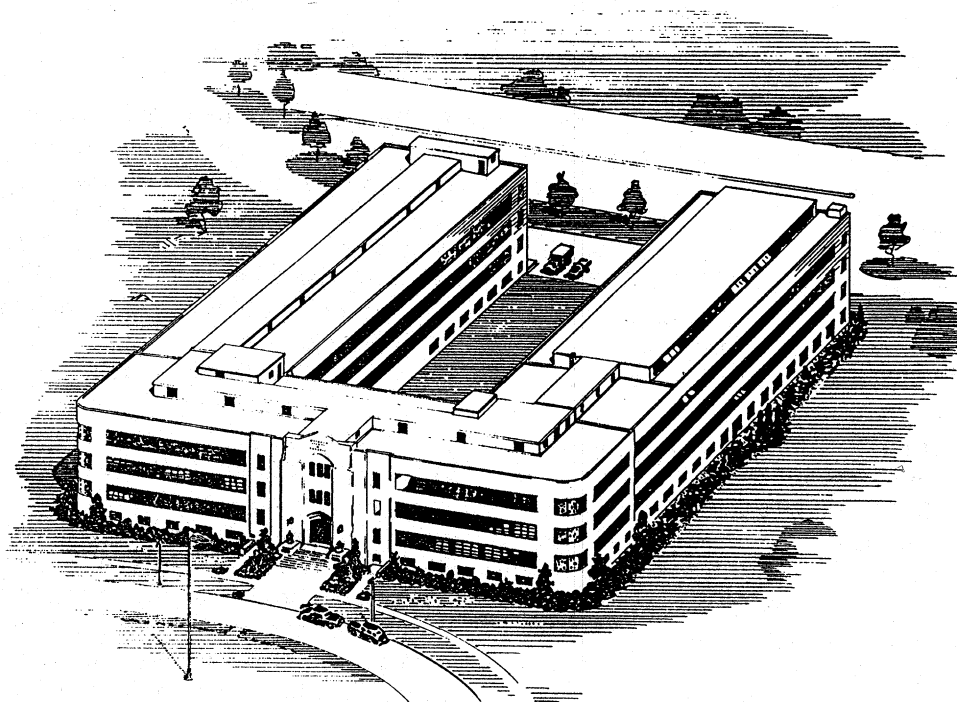


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SOME ESTERS OF GLUCOSE AND LACTOSE

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### Introduction

The lactose and glucose esters of the normal aliphatic acids containing an even number of carbon atoms, from acetic to stearic inclusive, and of propionic and benzoic acids, were prepared. The corresponding esters of sucrose are described in AIC-309. Since most of the lactose derivatives and some of the glucose esters had not been reported before, it was believed that many of them would be of general theoretical interest, as new compounds, especially if crystalline. Also it was thought that the esters might be useful as plasticizers, and this possibility was investigated.

### Description of Products

When first isolated, the acetates and the glucose benzoate were crystalline. The propionates through caprates inclusive were nearly water-white to light-amber sirups, some of which contained varying amounts of solid matter. Lactose laurate was a sirup containing a large proportion of solid matter. Glucose laurate, and the myristates, palmitates, and stearates of both sugars were waxy solids. Lactose benzoate was a brittle solid. The acetates, propionates, and butyrates were practically completely substituted. The higher esters retained some free hydroxyl, the glucose esters somewhat less than one group per molecule and the lactose esters a little more.

For final purification, the sirups, or the sirupy portions of the esters that consisted of both sirup and solid, were dissolved in three times their volumes of absolute alcohol, and enough water was added to precipitate part of the sirup. The precipitated sirups were concentrated *in vacuo* and dried over phosphoric anhydride and calcium chloride. The solid esters, either crystalline or waxy materials, were purified to constant optical rotation by recrystallization. The acetates were crystallized from 95 percent alcohol, the glucose benzoate from chloroform, the lactose butyrate from an alcohol-water mixture, and the other solids from alcohol-chloroform mixtures. Purification removed all the color from the solid esters, but of the sirups only the glucose butyrate became much lighter in color. The procedures removed most of the free acid and some of the incompletely substituted portions from the esters. With the exception of glucose stearate, the higher and lower members of the glucose series and the lower members of the lactose series were completely substituted. When allowed to crystallize slowly, the glucose laurate, myristate and palmitate, the lactose butyrate, and some of the lactose laurate formed needles. The glucose stearate and the lactose myristate, palmitate, and stearate appeared amorphous. The lactose benzoate was a transparent, brittle solid. The free hydroxyl and free acidity values are listed in Table I.

Table 1. Analyses of the Sugar Esters

Ester:	As isolated		Purified	
	OH groups per molecule	Free acidity, %	OH groups per molecule	Free acidity, %
<b>Glucose:</b>				
Acetate	0	0.2		
Propionate	0	0.05	0	0
Butyrate	0.05	6.1	0.15	0.6
Caproate	0.2	0.2	0.03	0
Caprylate*	0.6	10.6	0.3	1.1
Caprate*	0.8	12.2	0.2	1.1
Laurate	0.65	13.0	0	0
Myristate*	0.5	7.8	0	0
Palmitate	0.7	7.2	0	0
Stearate	0.2	3.4	0.3	Trace
Benzoate	0.1	1.0		
<b>Lactose:</b>				
Acetate	0	0.2		
Propionate	0.05	0.2	0	0
Butyrate*	0.04	3.9	0	0
Caproate*	1.3	4.6	0.8	0.85
Caprylate*	1.3	10.4	1.1	1.5
Caprate*	1.2	11.2	1.0	2.0
Laurate*	1.0	13.2	1.5	Trace
Myristate*	1.1	8.7	0.8	0
Palmitate*	1.2	7.4	0.5	Trace
Stearate*	1.4	10.5	0.8	Trace
Benzoate	0.6	10.3	0	3.2

\* Described as new compounds in J. Am. Chem. Soc., 73,4490 (1951).

The melting points of the laurates through the stearates increased with increasing acid chain length. The lactose esters had lower melting points than the glucose esters. Lactose laurate had an anomalously high melting point, possibly because of the larger amount of free hydroxyl present. In some cases, accurate melting points were difficult to obtain. The fused material was highly viscous and did not flow or release entrapped air bubbles until it had thinned out at higher temperatures (1).

In general the specific rotation decreased as the molecular weight increased. The lactose esters had considerably lower rotation than the glucose esters. Comparison with the data of Zemplén (2) and of Hess (3) indicates that the crystalline glucose laurate and palmitate are the  $\alpha$ -isomers. The glucose

myristate is also the  $\alpha$ -isomer, since it has an intermediate rotation and since the laurate, myristate, and palmitate have fairly constant molecular rotations of 47,500, 47,200, and 46,000, respectively. Undoubtedly, the noncrystalline products are mixtures of isomers.

The laurates through stearates were soluble in the nonpolar or fat solvents and insoluble in the polar solvents, with the exceptions that glucose stearate was only moderately soluble in ether and slightly soluble in petroleum ether<sup>1</sup> and that glucose laurate was soluble in acetone. Glucose acetate and lactose butyrate were soluble in both polar and nonpolar solvents; lactose acetate showed the same tendency but was less soluble. The sirups were much more soluble than the solid esters, being readily soluble in all the solvents except the 95 percent alcohol, in which solvent the higher ones were only slightly or moderately soluble. The best general solvents for the esters were benzene and chloroform.

The refractive index increased with increasing molecular weight. The lactose esters had a somewhat higher refractive index than those of glucose. A more detailed description of the products follows:

### Glucose

$\alpha$ -PENTAACETATE (4-7).--The mixture of pyridine, acetic anhydride and anhydrous  $\alpha$ -D-glucose was allowed to stand for eighteen days at 0° C. with occasional swirling. After two recrystallizations, long fine needles were obtained in 54 percent yield. Crystallization to constant rotation gave a product having the following properties<sup>2</sup>; m.p., 112.2-113.2°; specific rotation at 25°, + 95.9°; in ACS grade benzene,  $c = 4.1$ . (Literature values: 112-3° (4,7) and + 96.7° ( $C_6H_6$ ) (4) respectively.) The ester was soluble in 95 percent alcohol, acetone, ether, chloroform and benzene, and insoluble in petroleum ether.

PENTAPROPIONATE (3,6,8,9).-- $\alpha$ -D-glucose was treated with pyridine and propionic anhydride for nine days at 0° C. A pale straw-colored sirup was obtained in 88 percent yield. The purified sample had a refractive index of 1.4513 and a specific rotation of + 77.5°. (Literature values: (Sirups) specific rotations from +64.5° to +14.29° ( $CHCl_3$ ) (9).) The material was readily soluble in 95 percent alcohol, and in acetone, ether, chloroform, petroleum ether and benzene.

BUTYRATE (6,3).--The  $\alpha$ -D-glucose was treated with pyridine and butyric anhydride at room temperature for thirteen hours. The product, in 88 percent yield, was a light-amber sirup which contained a small amount of platelike crystals. On standing for several months, the sirup darkened. The purified sample had a refractive index of 1.4525 and a specific rotation of +51.8°. (Literature values: (Sirups) specific rotations of +52.04° ( $CHCl_3$ ) (3) and +44.5° ( $CHCl_3$ ) (6).) The material was readily soluble in all the test solvents.

1. THE PETROLEUM ETHER USED IN THIS WORK WAS A NORMAL HEPTANE PETROLEUM FRACTION WITH A BOILING RANGE OF 88 TO 98° C.
2. THE SPECIFIC ROTATIONS REPORTED IN THIS WORK WERE DETERMINED AT 25° C. IN ACS GRADE CHLOROFORM ( $c = 5$ ) (EXCEPT WHERE NOTED) WITH THE SODIUM D LINE. THE REFRACTIVE INDICES WERE DETERMINED AT 20° C. (SODIUM D LINE). ALL MELTING POINTS ARE CORRECTED.

PENTACAPROATE (3).-- The  $\alpha$ -D-glucose was treated with the acid chloride and pyridine mixture for eight hours at room temperature after the mixture warmed up (see General Methods of Preparation). An almost colorless sirup was obtained in 96 percent yield. The purified fraction had a refractive index of 1.4548 and a specific rotation of  $+58.4^\circ$ . (Literature values: (Sirup) specific rotation,  $+44.28^\circ$  ( $\text{CHCl}_3$ ) (3).) The material was readily soluble in all the test solvents.

CAPRYLATE.--The  $\alpha$ -D-glucose was treated with the acid chloride and pyridine mixture at room temperature for six hours. The product was a light-amber sirup containing a small quantity of particles with a crystalline appearance. The purified fraction had a refractive index of 1.4587 and a specific rotation of  $+46.8^\circ$ . This ester has not been previously reported. It was moderately soluble in 95 percent alcohol and readily soluble in chloroform and petroleum ether.

CAPRATE.--The  $\alpha$ -D-glucose was treated with the acid chloride and pyridine mixture at room temperature for seven hours. A quantitative yield of a light-amber sirup containing some whitish solid matter was obtained. The purified fraction had a refractive index of 1.4612 and a specific rotation of  $+40.3^\circ$ . This ester has not been previously reported. It was slightly soluble in 95 percent alcohol and readily soluble in acetone, ether, chloroform, petroleum ether and benzene.

$\alpha$ -PENTALAURATE (2,10).--The  $\alpha$ -D-glucose was treated with the acid chloride and pyridine mixture at room temperature for seven hours. A cream-colored, waxy solid was obtained in 92 percent yield. The recrystallized material melted at  $50.0$ - $51.4^\circ$  and had a specific rotation of  $+43.5^\circ$ . (Literature values:  $\alpha$ -form, m.p.  $48$ - $52^\circ$  (2), specific rotation of  $+40.62^\circ$  ( $\text{CHCl}_3$ ) (2);  $\beta$ -form, m.p.  $60$ - $66^\circ$  (2), specific rotation of  $+3.9^\circ$  ( $\text{CHCl}_3$ ) (2).) The ester was insoluble in 95 percent alcohol, soluble in acetone and chloroform and readily soluble in ether, petroleum ether, and benzene.

$\alpha$ -PENTAMYRISTATE.--The  $\alpha$ -D-glucose was treated with the acid chloride and pyridine mixture at room temperature for eight hours. A waxy solid was obtained in 88 percent yield. The recrystallized sample melted at  $59.0$ - $59.8^\circ$  and had a specific rotation of  $+38.3^\circ$  ( $+33.5^\circ$  in benzene). The ester has not been reported previously. It was insoluble in 95 percent alcohol and acetone, soluble in petroleum ether, and readily soluble in ether, chloroform and benzene.

$\alpha$ -PENTAPALMITATE (2,3,10,11).--The  $\alpha$ -D-glucose, acid chloride and pyridine mixture was held at room temperature for one hour and then heated to  $45^\circ \text{C}$ . for six hours. A tan, waxy solid was obtained in 89 percent yield. The recrystallized material melted at  $64.0$ - $65.0^\circ$  and had a specific rotation of  $+33.5^\circ$ . (Literature values:  $\alpha$ -form, m.p.,  $72$ - $75^\circ$  (2) and  $65$ - $67^\circ$  (3), specific rotation  $+29.7^\circ$  (2) and  $+34.30^\circ$  (3);  $\beta$ -form, m.p.  $68$ - $72^\circ$  (2) and specific rotation  $+4.6^\circ$  (2), (all in  $\text{CHCl}_3$ .) The ester was insoluble in 95 percent alcohol and acetone, soluble in petroleum ether and readily soluble in ether, chloroform, and benzene.

STEARATE. (2,3).--The  $\alpha$ -D-glucose, acid chloride (15% excess) and pyridine mixture was heated at 60° for nine and one-half hours. A nearly white, waxy powder was obtained from acetone solution in 76 percent yield. The purified sample melted at 66-71° and the specific rotation was +20.7°. (Literature values:  $\alpha$ -form, m.p., 70-71° (3) and specific rotation, +34.17° (CHCl<sub>3</sub>) (3);  $\beta$ -form, m.p., 72-78° (2) and specific rotation, +14.12° (CHCl<sub>3</sub>) (2).) The ester was insoluble in 95 percent alcohol and acetone, slightly soluble in petroleum ether, moderately soluble in ether, soluble in benzene and readily soluble in chloroform.

$\beta$ -PENTABENZOATE (12,13).--The  $\alpha$ -D-glucose, acid chloride (20% excess) and pyridine mixture was held at room temperature for one and one-half hours and at 60-80° for four and one-half hours. After recrystallization from alcohol-pyridine solution, the product was a white solid; the yield was 55 percent. The recrystallized product melted at 159° and the specific rotation was +23.5° (Literature values: m.p., 157° and specific rotation, +24° (CHCl<sub>3</sub>) (13).) The ester was insoluble in 95 percent alcohol, ether and petroleum ether, slightly soluble in benzene and moderately soluble in acetone and chloroform.

### Lactose

$\beta$ -OCTAACETATE (1).--The ester was prepared from  $\alpha$ -lactose hydrate by the sodium acetate-acetic anhydride method. It was obtained from ether-alcohol solution as needles or small prisms in 57 percent yield. The recrystallized material melted at 90-96°; the specific rotation was -24.25° (in ACS grade benzene,  $c = 10.3$ ). (Literature values: m.p., 90°; specific rotation, -23.52° (C<sub>6</sub>H<sub>6</sub>) (1).) The ester was insoluble in 95 percent alcohol, only slightly soluble in petroleum ether, slightly soluble in ether, fairly soluble in benzene and readily soluble in acetone and chloroform.

OCTAPROPIONATE (14).--The ester was prepared from  $\beta$ -lactose by the sodium acetate-propionic anhydride method. A light-amber, slightly turbid sirup, hard at room temperature, was obtained in 92 percent yield. The purified material had a specific rotation of +6.60°. (Literature value: specific rotation, +32° (CHCl<sub>3</sub>) (14).) The ester was slightly soluble in petroleum ether, soluble in 95 percent alcohol, and readily soluble in acetone, ether, chloroform, and benzene.

OCTABUTYRATE (15).--The  $\beta$ -lactose, butyric anhydride, pyridine mixture was kept at room temperature for eight hours and then heated to 50° for eight hours and 90° for twenty-three hours. When the product was worked up, a large quantity of crystals formed and were separated. A 35 percent yield of a light-amber sirup was also obtained. The recrystallized material (probably the  $\beta$ -isomer) melted at 77.0-77.4°, and its specific rotation was +4.6°, (-14.2° in benzene). The crystalline material has not been reported previously. The ester was readily soluble in all the test solvents.

CAPROATE.--The mixture of  $\beta$ -lactose, acid chloride (8% excess) and pyridine was held at room temperature for an hour after warming up and then heated to 70-80° for four hours. A light-yellow, slightly turbid sirup was obtained in quantitative yield. The purified material had a refractive index of 1.4646 and a specific rotation of +15.3°. This ester has not been reported previously. It was soluble in 95 percent alcohol and readily soluble in the other test solvents.

CAPRYLATE.--The mixture of  $\beta$ -lactose, acid chloride and pyridine was held at room temperature for one hour and then at 50° for five hours. An amber sirup was obtained in quantitative yield. The purified sample had a refractive index of 1.4650 and specific rotation of +14.5°. This ester has not been reported previously. It was moderately soluble in 95 percent alcohol and readily soluble in the other test solvents.

CAPRATE.--The acid chloride reaction mixture was kept for one hour at room temperature, three hours at 50° and six hours at 60°. An amber, slightly turbid sirup was obtained in 95 percent yield. Spherical particles formed in the sirup after it had stood for several months. The purified sample had a refractive index of 1.4657 and a specific rotation of +12.6°. This ester has not been previously reported. It was slightly soluble in 95 percent alcohol, and readily soluble in the other test solvents.

LAURATE.--The acid chloride reaction mixture was heated to 60° for ten hours. An amber sirup containing a large proportion of solid matter was obtained in 88 percent yield. The purified solid melted at 110-112°, and the specific rotation was +13.4°. This ester has not been reported previously. It was insoluble in 95 percent alcohol, almost insoluble in petroleum ether, moderately soluble in acetone and ether, and readily soluble in chloroform and benzene.

MYRISTATE.--The acid chloride reaction mixture was heated to 60° for ten hours. A cream-colored, waxy solid was obtained in 81 percent yield. The purified solid melted at 43.4-46.0° and the specific rotation was +9.41°. The ester has not been reported previously. It was insoluble in 95 percent alcohol and acetone, fairly soluble in petroleum ether, and readily soluble in ether, chloroform and benzene.

PALMITATE.--The acid chloride mixture was heated at 70° for eleven hours. A tan, waxy solid was obtained in 94 percent yield. The purified material melted at 55.6-58.2° and had a specific rotation of +9.01°. This ester has not been reported previously. It was insoluble in 95 percent alcohol and acetone, but readily soluble in the other test solvents.

STEARATE.--The acid chloride (15% excess) mixture was heated to 70° for thirteen hours. A light-tan, waxy solid was obtained in 93 percent yield. The purified sample melted at 62.5-64.5° and had a specific rotation of +7.92°. The ester has not been reported previously. It was insoluble in 95 percent alcohol and acetone, soluble in ether and petroleum ether and readily soluble in chloroform and benzene.

BENZOATE (16).--The acid chloride (20% excess) mixture was held at room temperature for one hour and then heated at 60° for five hours. A brittle, amber, transparent solid was obtained in quantitative yield. The purified sample had a specific rotation of +49.4°. It was insoluble in petroleum ether, moderately soluble in 95 percent alcohol, and readily soluble in other test solvents.

## General Methods of Preparation

The lactose acetate and propionate were prepared by using acid anhydride and sodium acetate according to the method of Hudson and Johnson (1). The acid anhydride (70% excess) with pyridine (1.9 moles per mole of anhydride) as a catalyst, was used for the preparation of the other esters of the lower fatty acids. The reaction mixture was precipitated in ice water or concentrated under reduced pressure. Then the ester was washed in ether solution with dilute hydrochloric acid, bicarbonate solution, and finally with water; dried and filtered. The volatiles were removed at 60° C. under a pressure of less than 3 mm. of mercury.

For the higher esters, the acid chloride (10% excess) and pyridine (1.1 moles per mole of acid chloride) were used in chloroform solution (2). The acid chlorides were distilled before use. A chloroform solution of the acid chloride was added dropwise to the stirred mixture containing the sugar, pyridine and part of the chloroform; the whole was cooled by an ice-salt mixture. The reaction mixture was kept cool for one hour after the acid chloride had been added, then various temperatures were used, depending on the reaction rate. The reaction mixture was concentrated somewhat under reduced pressure, ether was added to precipitate the pyridine-acid chloride complexes, and the mixture was filtered. The ether solution was washed and dried, and the volatiles were removed in a manner similar to that used for the acid anhydride-pyridine treatment. The yields of sirups and waxy compounds were approximately 85-95 percent of the theoretical yields. The crystalline compounds were obtained in about 55 percent of the theoretical yield.

We are indebted to Mrs. Ruth Kelly for the free acidity and free hydroxyl (17) determinations. Saponification methods mild enough to avoid the alkaline degradation of the reducing sugars did not saponify the higher esters.

## Plasticizing Action of the Esters

The esters (as first isolated) were tested as plasticizers for Vinylite VYDR, a polyvinyl chloride-acetate, by T. J. Dietz and coworkers. The results are listed in Table II. Unsatisfactory esters are not included. Results with dioctyl phthalate are reported for comparison. The glucose butyrate and caproate gave the best results, but they were not so efficient as dioctyl phthalate, and they gave dark-colored mixtures.

The lower esters also were **tested** as synergists with tricresyl phosphate. The results obtained with a 50-50 mixture by weight of ester with tricresyl phosphate are listed in Table II. The plasticizing effect of the series was increased, but the mixtures tested were still not as efficient as the controls. Again glucose butyrate and caproate had more plasticizing effect than the other esters.



Table II. Tests of Esters as Plasticizer for Vinylite VYDR<sup>a</sup>

Ester	Compatibility <sup>b</sup>		Tensile strength, psi		Modulus (100%, psi)		Elongation, %	
	a	b	a	b	a	b	a	b
<b>Glucose:</b>								
Acetate	C	?	-	3460	-	-	-	135
Propionate	C	?	5170	3850	-	2680	-	180
Butyrate	C	C	3430	3990	3115	2690	280	280
Caproate	C	C	3400	3620	2495	1930	290	280
<b>Lactose:</b>								
Acetate	C	?	-	4580	-	-	-	≤10
Propionate	I	?	5810	3800	-	-	-	60
Butyrate	I	C	4803	3390	-	3160	-	260
Caproate	-	C	-	3500	-	2500	-	290
<b>Controls:</b>								
Dioctyl phthalate	C	C	3115	3030	1300	1245	400	300
Tricresyl phosphate	-	C	-	3215	-	1625	-	290
50% DOP + 50% TCP	-	C	-	3290	-	1490	-	370

a/ a = sugar esters; b = mixtures of sugar ester and tricresyl phosphate

b/ C = compatible; I = incompatible; ? = doubtful compatibility.

### Summary

A series of glucose and lactose esters were prepared and characterized. Those not previously reported in the literature include glucose caprylate and caprate and lactose caproate, caprylate and caprate (obtained as sirups); lactose laurate, myristate, palmitate, and stearate (obtained as solids); and  $\alpha$ -D-glucose pentamyrystate and lactose octabutyrate (obtained as pure, crystalline compounds). The acetate, propionates, butyrates, and benzoates of glucose and lactose, and glucose laurate, palmitate, and stearate have been reported previously. As plasticizers for Vinylite VYDR, glucose caproate and butyrate gave the best results of the series.

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